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October 21, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket 97D-0433
Average, Population, and Individual Approaches to Establishing Bioequivalence

Dear Sir/Madam,

The draft guidance for industry entitled "Average, Population, and Individual Approaches to Establishing Bioequivalence" (September 8, 1999, FEDERAL REGISTER, pages 18842 – 18843) was reviewed by the U.S. Clinical Pharmacology and Clinical Biostatistics divisions at Pharmacia & Upjohn.

As stated in previous comments to the FDA on the preliminary draft guidance on this topic which issued in 1997, it is still our concern that the recommendation to move away from the current average bioequivalence (ABE) criteria is not based upon a documented public health risk. The new procedures recommended in the draft guidance are more complex, costly, and will require additional drug exposure. With the exception of drugs with high intersubject variability and/or a narrow therapeutic index, individual bioequivalence (IBE) is not clinically justifiable for most drugs. In recent public workshops, meetings, and at the Pharmaceutical Sciences Advisory Committee meeting, presentations from the FDA and from members of the expert panel on bioequivalence (BE) have failed to justify the change from average to individual BE. Additionally, IBE represents a departure from global harmonization on BE methodology.

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Our specific comments on this guidance are outlined below.

1. V.A.1. Replicated Crossover Designs
   Alternative study designs can be used to estimate functions of variance components for individual BE. In the recent AAPS International Workshop on IBE, Lawrence Gould presented such an approach which utilizes a 2 x 2 crossover design. The guidance should allow for the use of simpler study designs rather than specifying only the four-period, two-sequence, two-formulation design.

2. V.C. Sample Size and Dropouts
   The requirement to estimate study sample sizes for IBE or population bioequivalence (PBE) by simulation is problematic and burdensome. Consideration should be given to expanding Appendix C to include recommended number of subjects for additional variance values. The second paragraph of this section provides specific recommendations, many of which don't make sense and appear to be contradictory, on addressing dropouts in the protocol. Especially in the case of a replicated study design, there are several possible scenarios in which dropouts and potential replacement subjects complicate the analysis. We suggest that the wording be modified to state that specific procedures for handling dropouts using acceptable methodology should be defined in the protocol.

3. VI.B.2.c. Replicated Crossover Designs
   This section lacks a recommended SAS procedure for the PBE analysis. An example of SAS program statements should be included in an appendix to assure consistency among sponsors in calculation of confidence interval bounds.

4. VI.B.3. Individual Bioequivalence
   This section lacks a recommended SAS procedure for the IBE analysis. An example of SAS program statements should be included in an appendix to assure consistency among sponsors in calculation of confidence interval bounds.

5. VII.C. Outlier Considerations
   If one uses the proposed replicate study design with ABE for determination of BE, the BE limits could be greatly affected by outliers for both replicates of the test and reference products. This could result in an inflated variance, and more subjects would be needed to establish BE. Thus, it is likely that the replicate study design for ABE will require more subjects than proposed in the guidance, resulting in increased costs and subject exposures.

6. VII.D. Discontinuity
   The difference in confidence interval width at the changeover point from constant- to reference-scaling is troublesome. Further direction or specific recommendations should be provided for dealing with this situation before publication of this guidance.

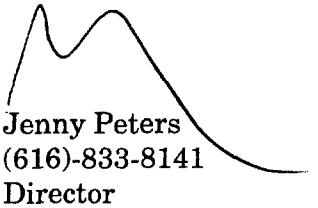
7. Appendix C, Sample Size Determination
   The requirement to use simulated data for sample size determination for PBE and IBE is burdensome. More detailed procedures and tables should be included in this appendix.

We appreciate the opportunity to comment on this draft guidance and look forward to continued industry participation in formulating scientifically valid and clinically relevant regulatory policy in this area.

Please let us know if you have any questions on our review.

Sincerely,

Pharmacia & Upjohn Company



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